NOVARTIS

Judith M. Sills
Executive Director
Safety Intelligence

Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936
Tel: 862-778-2472
Fax: 973-781-8477

July 6, 2004

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Novartis Comments on FDA Draft Guidance for Industry: Pre-marketing Risk Assessment

Docket No. 2004D-0187

Dear Sir/Madame:

Novartis Pharmaceuticals Corporation is an affiliate of Novartis AG (NYSE: NVS), a world leader in pharmaceuticals and consumer health. Headquartered in Basel, Switzerland, Novartis Group companies employ more than 78,000 people and operate in over 140 countries around the world.

Novartis Pharmaceuticals Corporation researches, develops, manufacturers and markets leading innovative prescription drugs used to treat a number of diseases and conditions, including central nervous system disorders, organ transplantation, cardiovascular diseases, dermatological diseases, respiratory disorders, cancer and arthritis.

Novartis and the FDA share a mutual interest in making safer and more effective products available to patients as rapidly as possible, as well as ensuring their appropriate use and minimizing the occurrence of preventable adverse events. As one of the world's largest pharmaceutical companies, Novartis commits extensive resources to developing drugs and bringing them to market. It is essential that FDA ensure that its policies and expectations regarding risk management are clear and transparent to all stakeholders, and that the standards are consistently applied. We appreciate the opportunity to provide comments on the draft guidance documents.

General Comments

Novartis positively acknowledges FDA's effort to reflect the public comments it has received on the Pre-marketing Risk Assessment Concept Paper. In particular, we are pleased that FDA has placed increased emphasis on the following points in the document:

- It is neither possible nor realistic to identify all risks prior to approval; the goal is to achieve an acceptable balance between benefits and risks.

2004D-0187 C4

- All products are not the same; many of the recommendations in the guidance are not intended to be generally applied to all products.

- Risk assessment should be addressed in a proactive, systematic manner and decisions based on scientific evidence.

- There must be close interaction between the sponsor and the Agency during the Development process to discuss potential safety concerns.

In addition to close collaboration between the sponsor and the individual Review Division, the Agency must also ensure that evaluation of safety issues and requirements for additional safety studies and risk management activities be handled in a consistent, transparent manner between Divisions and across Centers. This is particularly critical in situations where FDA mandates additional safety studies prior to approval, a RiskMAP prior to marketing, or other requirements beyond that recommended by ICH, We believe that such requests for such studies be made only when specific risks have been identified and when there exist clear areas of public health concern. In addition, it should be clear that such data would be critical to make better decisions about patient safety. While these actions are within the purview of FDA, it must again be emphasized that all products are not identical, the need for and types of risk management activities should be considered on a product-by-product basis.

FDA has stated publicly that they will take the approach of evidence-based decision making, which we support. However, decisions to require additional studies and increased amounts of data pre-approval should be made only in exceptional circumstances and should not be made with the goal to identify as many risks as possible prior to approval. It should be kept in mind that additional and/or larger studies may result in unnecessary costs and delays in drug development, and ultimately will delay getting needed medicines to patients. Moreover, several items in the draft guidance have the potential to establish a new standard for approval of products, especially those that are not first in class or a unique therapy. For each of the draft Guidance documents, we request that FDA explicitly state that the document does not expand or otherwise supplement the regulations. We do not believe that the FDA "disclaimer" as written is sufficient. Of particular concern are the following concepts:

- Emphasis on the desirability of data from active comparator drug if "an acceptable alternative" treatment exists. In addition to the above comments, this requirement exceeds FDA's mandate to approve drugs solely on the basis of their individual safety and efficacy.
- Suggestions for situations when the size of the safety database should exceed recommendations set forth in ICH E1.
- Delaying final dose selection until Phase III will increase the size, complexity, and time to complete these trials. It will also increase the risk of patients receiving an inadequate or sub-optimal dose, potentially impacting subject participation because of the additional risk of being exposed to inappropriate doses.
- Requirements for including placebo arms in long-term controlled safety studies may raise concerns regarding the ethical issues associated with this practice in some circumstances.
- The suggestion that in certain situations, large simple safety studies (LSSS) may be a pre-approval requirement.
- Non-specific proposals for pre-marketing activities by sponsors intended to reduce potential medication errors.

Specific Comments

Section: II.B. Overview of the Risk Management Guidances

Line(s)	Comment
45-51	FDA should acknowledge that formal Risk Management is an evolving field and that the value of specific risk management tools has yet to be definitively established.
56-67	Line 56 notes that many recommendations in this draft guidance are not intended to be generally applicable to all products. However, within this draft guidance, it is often unclear when the concepts should be generally applicable and when they should not. We suggest that the final guidance be specific about those expectations that should be applied to all products and criteria for determining when special considerations should apply. Adding clarity on how to determine when to incorporate specific points into a development plan will greatly enhance the value of this guidance.
65	Clarification is needed on what is meant by an "unusual type or level of risk".

Section III. The Role of Risk Assessment in Risk Management

Line(s)	Comment
106-108	The population of patients chosen for study also affects the adequacy of risk assessment. We recommend the sentence be modified to read, "The adequacy of this assessment is a matter of both quantity....and quality (the appropriateness of the assessments performed, the adequacy of the patient populations studied and how the results are analyzed)."

Section: IV.A. Size of the Pre-marketing Safety Database

Line(s)	Comment
146 - 147	The document states that "some risks become apparent only when a product is used in tens of thousands or even millions of patients in the general population." We request that FDA explicitly acknowledge that this "fact" does not in any way cast doubt, or undermine, the NDA approval process or the studies done in support thereof, or that the approval of a NDA is in any way "conditional".
155 and 226	Under the Federal Food, Drug, and Cosmetic Act, FDA must evaluate safety and effectiveness solely with respect to the drug under review, and not against existing therapies. In addition, we do not agree that the appropriate size of the safety data base should depend on the potential advantages of the product over existing therapy for the following reasons: (1) it is not possible to determine all the "potential" advantages of a product at any given time – many are discovered by serendipity, others are determined in research; (2) older products may not have received sufficient scrutiny to determine their true characteristics, positive and negative, so comparisons may be impossible; (3) comparator drugs are not a viable option for those who cannot tolerate them, so comparisons with a new drug may be meaningless. We request that these bullet points be deleted.
160	The Agency makes reference to symptomatic treatment of non-serious diseases. Although many diseases may be viewed by some as "non-serious" they may have a dramatic impact on quality of life and in some cases are associated with disability. We recommend that the first use of the term non-serious be defined as "diseases that are not life-threatening or not associated with major irreversible morbidity".
164-173	We are supportive of language that reflects a flexible approach to be applied when a drug is for acute use or holds promise for the treatment of life-threatening or severely debilitating illnesses. There is higher tolerance for risk (known and unknown) in the treatment of life-threatening or severely debilitating illnesses, particularly when no suitable alternative exists and there is evidence of clinically

	meaningful benefit. It should be acknowledged that even small benefits to an otherwise untreated or under-treated patient population may change the acceptable benefit to risk balance.
175	We request clarification on the Agency's definitions of "chronic use" and "short term use".
183-189	Although we feel that FDA has improved the description of patients who should comprise the 1500 subjects recommended under the ICH E1 guidance, the use of the terms "relevant doses" and "reasonable representation" are vague and subject to broad interpretation. It would be helpful if FDA could be more specific or provide a useful illustration of the Agency's general expectation. It is also not clear whether the recommended size strictly refers to exposure at dosage levels intended for clinical use and whether patients exposed to dose levels lower than the intended levels could not be a part of the recommended size of exposure. Furthermore, while data from doses higher than those proposed for marketing may be informative, it may not be appropriate for drugs with a narrow safety margin, as it may put patients at increased risk for toxicity.
203-206	It should be acknowledged that aggregated data from clinical trials often have insufficient power to estimate the frequency of rare events. Accordingly, issues regarding low-frequency events or SAEs may more appropriately be followed up with post-marketing activities rather than by arbitrarily increasing the size of the pre-marketing safety database. With regard to the statement that expected low-frequency adverse events must be quantified where an adverse event has been observed in similar products, individual drug sponsors may not have access to clinical information known to FDA from other investigational drugs. We request the Agency provide examples of recent use of this approach and the outcome.
215-218	The guidance document states "...clinical trials should be designed with a sufficient number of patients to provide adequate statistical power to detect pre-specified increases over the baseline morbidity or mortality". It is not clear whether "pre-specified increases over the baseline morbidity" refers to the increases over the background rate of morbidity or within-patient changes in morbidity from baseline. In addition, Novartis believes that the needed sample size will depend very much on what the "pre-specified increase" over the baseline morbidity or mortality is determined to be and that the required sample size can be very high if the increase is small. An exponential increase in the size of the safety database may not add substantially to patient safety but will add substantially to development time. Guidance on acceptable pre-specified increases in various settings is requested.
220-234	We note that FDA has retained in the draft guidance two additional situations when safety databases should be larger than described under ICH E1. In the first circumstance, increasing the size of the database above the ICH requirement without specifically defining the concern or objective is not likely to significantly add to an assurance of patient safety. As noted in the General Comments, the second circumstance described ("a safe and effective alternative...is available") is of particular concern since it potentially introduces a new standard for approval. In this situation, if a drug is not first in class or unique therapy for a specific disease, the language implies that a larger safety database than required under ICH E1 may be required by FDA prior to approval. Under the Federal Food, Drug, and Cosmetic Act, FDA must evaluate safety and effectiveness solely with respect to the drug under review. As indicated in our previous comments (line 155), we request that this bullet be deleted. The Agency should explicitly state that the document does not expand or otherwise supplement the regulations and that the sponsor is required only to provide sufficient data for

	the Agency to conclude that the drug is safe and effective for its labeled indication. FDA's authority to consider the safety and/or effectiveness of other marketed drug products is limited to instances where a known health risk is associated with a drug class (e.g., non-sedating antihistamines) or when the applicant proposes comparative safety or efficacy claims in the product labeling. In the absence of such comparative claims, the existence of a "safe alternative" should make no difference in determining whether a larger database could be appropriate. Novartis also requests guidance to address how many fold increase the pre-registration database will need to be if there is no specific safety signal that is being examined, i.e. how will even a 2-3 fold increase in database size be used to better define the risk of extremely rare events? The qualifying language that appears on lines 228 to 234 does not adequately address this concern. Before the Agency requests a larger database prior to approval, there should be clear criteria for determination of a concern (e.g. a "gold standard" via therapeutic guideline) to avoid arbitrary determinations motivated by a variety of factors besides safety.

Section: IV.B. Considerations for Developing a Pre-marketing Safety Database

Line(s)	Comment
252-271	The draft guidance states "control groups may be given a placebo or an active comparator, depending on the disease being treated" (line 256). This is a complicated issue that needs to be carefully considered. Placebo controls in chronic diseases are often associated with ethical issues, declines in enrollment, and missing data problems due to dropouts. FDA states that the usefulness of active comparators in long-term studies depends on the adverse events of interest. This statement is vague and the examples provided on lines 262 through 271 do not adequately demonstrate the value of the Agency's proposed emphasis on comparative data. Since it is often not possible to detect rare events prior to approval, we suggest that FDA describe how such an approach has been successfully applied and why post-approval risk assessment activities would not be appropriate (e.g., illustrate a specific case study; describe the hypothesis tested and what definitive information was obtained). If long-term safety studies are conducted against an active comparator, FDA should not require that the sponsor power the studies for comparative safety purposes, and the guidance should reflect how these results might be described in the labeling.
279-292	Novartis agrees with the need to broaden inclusion/ exclusion criteria. However, this will also require increased sample size, as the assessment of both efficacy and safety will be more difficult because of the increased number of potential confounding factors. It should be kept in mind that there may be a trade-off between diversity and analyzability. Inclusion of diverse populations requires sufficient numbers of those patients to allow the data to be meaningful. This will have the cumulative effect of significantly increasing the number of studies and study subjects needed for drug approval. Additionally, it may not be feasible to recruit and retain such numbers in all situations. For some high-risk populations, it may not be desirable to expose subjects to a drug whose effects are not fully defined at the end of Phase II. Regarding evaluation of data on diverse populations, consideration should be given to giving a higher weight to the population in which the disease is most expressed. Novartis suggests that FDA reconcile this guidance to the current guidance in effect for gender, race, and age diversity in a pre-registration database and add clarification as to how this will add to our knowledge in small subgroups
307-318	Novartis believes that dose ranging in Phase III should be considered on a case-by-case basis, based on the characteristics of the drug, disease, and Phase II findings. Using a range of doses in Phase III will:

	1) result in less data on the dose that is ultimately marketed unless the trials are significantly larger; 2) Significantly increase the size of Phase III programs if we want to maintain reasonable power in comparing efficacy between doses and the comparator. 3) Potentially lead to requests for multiplicity adjustment because of the inclusion of multiple doses for efficacy evaluations; and 4) Result in more three or four armed phase III studies, requiring a dramatic increase in subjects. Consequently, Phase III dose ranging requirements would not only increase the time and complexity of product development, but would also expose more clinical trial subjects to potentially inadequate doses (in a balanced four arm study, only one in four patients would receive the potentially optimal dose). Similarly, examination of exposure-response relationships in phase III should be undertaken on a case by case basis and in general should only be undertaken when there is sufficient evidence that the range of expected exposures in the trial would be adequate to define an exposure-response relationship. Lines 316-318 state that demonstrating a dose-response relationship in late phase clinical trials could add important information to the assessment of efficacy. We believe that late phase clinical trials are generally too late in the development process to examine dose-response relationship. By this time, adequate dose-response examination should have been performed and the final dose(s) selected for commercialization.

Section: IV. C. Detecting Unanticipated Interactions as Part of a Safety Assessment

Line(s)	Comment
342-343	While Novartis recognizes the potential value of understanding product-disease interactions, the reality of determining these in a practical manner is clearly a challenge. Examples of the Agency's thinking and expectations would prove useful in this section
345	There are a myriad of dietary supplements available to the public, including some that have been associated with significant adverse effects, either alone or in combination with prescription drugs. Such products do not require a prescription and it is difficult to know what products are "commonly used" by prospective patients, or "likely to be co-administered". This is especially true when designing global trials, as product availability and preferences may differ by country.
356-361	We suggest that reference to population pharmacokinetics (PK) make it clear that data should be obtained via a directed investigation with planned objectives and analyses. *Post hoc* analyses (for unanticipated adverse events or drug interactions) are problematic since information needed to do such analyses may not have been appropriately collected up front. There should be clearly defined criteria when population PK approaches are relevant/needed to avoid having the expectation that every study would include a PK component.
363	To be consistent with other recent FDA guidelines, we suggest that this sentence be revised to state"...one or more well-established and valid biomarkers pertinent..." This clarity is needed to avoid confusion in cases where a sponsor is developing a potential safety biomarker.

Section: IV. D. Developing Comparative Safety Data

Line(s)	Comment
368-397	Despite FDA's statement that comparative safety trials "generally are not necessary," we remain concerned that the general discussion could "open the door"

	for the Agency to request comparative trials on a more routine basis. As discussed in our general comments, this would represent a new standard for approving drug products that goes beyond the statutory requirements. We thus suggest removing this section. The Draft Guidance infers that comparative clinical trials would enable an accurate assessment of relative risk. This is not necessarily true as clinical trials are powered to meet primary efficacy objectives. In the case where comparative efficacy claims are sought, as suggested in lines 393-397, the sample size may not be adequate to characterize adequately the safety advantages or disadvantages. Furthermore, it should not be the expectation that studies for comparative efficacy claims be powered to demonstrate both efficacy and safety objectives, as this has the potential to substantially increase the size, complexity, and cost of individual studies. The Draft Guidance also suggests that if there is a well-established related therapy, comparator trials would be desirable in certain situations. Novartis recommends that when there are diseases or categories of drugs where FDA feels that a specific public health objective can be realized by conducting comparative trials, the Agency should develop a specific guidance applicable to the disease and/or therapeutic class. This will allow for transparency of the criteria applied, allow for sufficient external scientific input as part of the guidance development process, ensure that consistent requirements are applied to all sponsors, and facilitate predictable development plans. The guidance should describe the Agency's expectations regarding statistical design features of comparator trials that would achieve the objective intended by this section. On line 376, the Agency's intent with respect to characterizing background rates is not clear. As written, this could mean morbidity associated with the natural history of the disease, co-morbidities, or morbidity associated with concomitant therapies. On lines 378 to 380, FDA suggests that results from a single-arm study with a high rate of adverse events would suggest the need for a three-arm trial of the investigational drug compared to a comparator and placebo. We question the value of this approach if the sponsor has conducted placebo-controlled trials, and epidemiological studies or other data sources have established the background rate of co-morbidities or adverse events associated with alternative treatment options. We suggest that the second bullet ("there is a well-established related therapy") be deleted. Even if there is a well-established therapy, there will always be a subset of the population for whom the well-established therapy is not effective or well-tolerated and the new therapy may be useful. In the event that this bullet is retained, we suggest that the language on line 382 be changed to: "There is an alternative treatment available with a well-established benefit-risk profile." There are many "well established" therapies that have not been proven to be efficacious via controlled clinical trials.

Section: V. A. Risk Assessment During Product Development

Line(s)	Comment
443-463	A pre-approval requirement of a large simple safety study (LSSS) is a significant burden that should be reserved for only those cases when a signal suggests a possible serious adverse event that if substantiated would result in a significant public health risk and prevent product approval. A pre-approval requirement for an LSSS is not a trivial requirement as it represents a *de facto* fourth phase to

	development. It would be difficult to design an LSSS study until evidence of efficacy in Phase III had been obtained. On line 450, FDA indicates that an LSSS is most commonly performed as a phase IV commitment, but then goes on to describe possible reasons for conducting a pre-approval LSSS (lines 454 to 463). No examples of when a post-approval LSSS might be considered are outlined. Conducting an LSSS is a significant commitment at any stage of the product life-cycle. In addition, we suggest that the first sentence of the paragraph that begins on line 460 be revised to read: "When there are early signals (i.e., pre-clinical or clinical) of serious toxicities or other unique or special considerations (e.g. regarding the safety of the use of the product with a concomitant medication where the previous clinical data have not addressed the issue sufficiently) that are not likely to be sufficiently resolved by the available data and are unlikely to be sufficiently addressed by the remaining ongoing studies". We also request that FDA include a reference that describes considerations for LSSS design features consistent with current FDA expectations.

Section: V.B. Risk Assessment and Minimizing the Potential for Medication Errors

Line(s)	Comment
473-517	The guidance is requesting an extensive pre-marketing risk assessment regarding possible medication errors. It is not clear if this is a request for development programs generally or if this would be only for certain circumstances or types of products. Potential medication errors were discussed in detail in the industry comments to the FDA regarding the March 2003 proposed safety reporting regulations (the "Safety Tome"). In addition to the comments we submitted on the "Safety Tome", we would like to highlight that it is not appropriate for FDA to attempt to effect changes in existing regulatory standards via guidance documents. In addition, this guidance is not the appropriate vehicle to deal with specific details surrounding medication error prevention analysis (MEPA). A more appropriate vehicle for presenting Agency recommendations on this subject would be the "specific and expanded guidance on medication error prevention analysis" referenced in text lines 512 and 513. This would help ensure regulatory consistency across various guidance documents that deal with medication errors. This guidance document and plans for the guidance on medication error prevention analysis (MEPA) appear to ignore the recommendations from the December 4, 2003 meeting of the Drug Safety and Risk Management Advisory Committee, which recommended delaying issuance of a guidance until appropriate outcomes data could be developed.

Section: V.C. Safety Aspects that Should be Addressed During Product Development

Line(s)	Comment
519-559	We are concerned that the proposed guidance states that <u>all</u> drug development programs should include assessments for QTc prolongation, liver toxicity, drug-drug interactions, polymorphic metabolism, as well as two new additions, nephrotoxicity and bone marrow toxicity. Since some products will have no potential for some of safety issues discussed in this section (e.g. non-absorbed drugs will have no potential for QTc prolongation), we recommend that there be a discussion about these potential issues during drug development, but that there not be an absolute requirement for such assessments. Although FDA states that these would not always involve the generation of data, it is not explained when pre-clinical studies or other data could be appropriate. We suggest that the clarifying language, "as

	appropriate" be added to the introductory sentence in this section (line 521).

Section: VI. Data Analysis and Presentation

Line(s)	Comment
564-567	This section should also include reference to the ICH Guidance for Industry M4E. We believe this document, combined with ICH E3, has effectively superseded FDA's 1988 guidance and contains the most current information on how clinical safety data should be integrated, organized and presented in NDAs. We assume that the new considerations related to coding, temporal associations and dose effect are best addressed within the Summary of Clinical Safety in Module 2 of a CTD formatted NDA.

Section: VI.A. Describing Adverse Events to Identify Safety Signals

Line(s)	Comment
569	This section focuses exclusively on clinical AEs. We believe it should also address adverse events measured by laboratory parameters and other biomarkers.
581	The guidance states that sponsors should use one coding convention or dictionary throughout a clinical program, but does not explicitly mention that this takes into account updating the MedDRA dictionary as new versions become available. We would appreciate confirmation of this assumption.
603	We request that FDA provide clarification regarding whether consultation with the FDA to re-characterize an event to make it consistent with accepted case definitions should be conducted "real-time" or as a group review at the time of integrated analysis of a clinical trial or development program (i.e. post database lock).
640-675	The relative strengths and weaknesses of "splitting" versus "lumping" coding practices are well described. To some extent, MedDRA already contains some pre-specified groups that are searchable using the special search term facility. One of the challenges with pre-specified groups is that they need to be reconsidered with every MedDRA version change. Furthermore, to make "constellations" or "groups" of certain adverse events useful and interpretable, uniformity is needed for drugs in the same class and perhaps, for drugs across classes. We would appreciate it if FDA would provide examples of grouping approaches using MedDRA. In addition, Novartis recommends that FDA establish and make publicly available groupings of MedDRA terms that would serve as case definitions for commonly reviewed signals and adverse events.

Section: VI.B. Analyzing Temporal or Other Associations

Line(s)	Comment
679 - 680	The text states that for individual safety reports, the temporal relationship between product exposure and adverse event is a critical consideration in the assessment of causality. Given the inadequacy of data in individual safety reports, application of causality algorithms to a single case is fraught with misinterpretation. It is almost impossible to rule out with certainty the likelihood that the suspect drug may have contributed to an adverse experience. Therefore, most adverse experiences at the individual case report level end up with a possible association. With the exception of cases involving a positive rechallenge, there is little or no advantage in performing causality assessment on individual case reports. Although a series of cases may be used to generate hypotheses concerning the association between an adverse experience and drug exposure, there is no methodology determined to date that is reliable and reproducible for individual causality assessment. Thus, causality assessment at the individual case level is open to a high likelihood of misinterpretation. We recommend that FDA delete all text suggesting that causality

	can be determined through assessment of individual safety reports.
690-691	Because there are many occasions where increasing event rates do not suggest causality, and there are occasions where causally related adverse event rates decrease over time as indicated on line 698-699, we suggest that the example "(e.g., an increasing rate of events over time could suggest causality)" be deleted.
691 – 693	Please clarify "the relative importance of differences in adverse event frequencies between study groups". For example, does the statement refer to situations where the differences in frequencies between study groups may appear to be small, but the temporal patterns are significantly different?
736 - 738	Recommendations are provided to establish cutpoint above and below a given body weight dose; however, the relevance of this depending on the strength of the PD dose-AE relationship is not made. We request clarification on this point.

Section: VI.C. Analyzing Dose Effect as a Contribution to Risk Assessment

Line(s)	Comment
756	While "cut point" analyses appear to be useful there may not be enough patients in the border zones to permit valid statistical analyses.

Section: VI.E. Using Pooled Data during Risk Assessment

Line(s)	Comment
806-811	There are areas where placebo-controlled studies are not ethical and all randomized trials employ active comparators. It would be helpful to mention the pooling principles for such areas.
835 - 837	We would appreciate guidance on how safety data collected during Phase II or III crossover trials should be included in the pooled analysis. One may consider allocating all safety information collected from the start of a treatment up to the intake of subsequent treatment given an adequate washout period, or consider data from the first period only.

Section: VI.F. Rigorous Ascertainment of Reasons for Withdrawals from Studies

Line(s)	Comment
864-870	While we agree with the objective of rigorous ascertainment of reasons for withdrawal from studies, the language in this section appears to presume that sponsors will have ongoing access to follow-up information for subjects who choose not to participate. Despite best efforts this may not be the case, even in situations when withdrawal was the result of an adverse event (e.g., in cases of threatened litigation, further requests for follow up information may be denied). The draft guidance should reflect that follow-up information should be diligently pursued but if access is denied or not possible, the sponsor's efforts should be recorded in the case report forms.

Section: VI.G. Long-term Follow-up

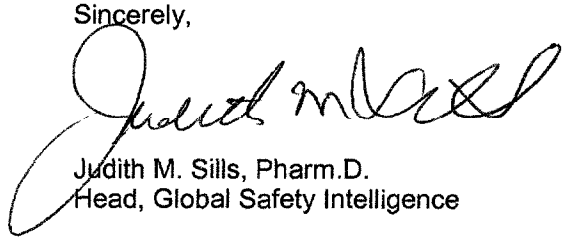
Line(s)	Comment
874 - 881	We acknowledge the importance of long-term follow-up in some circumstances; however, we are concerned with its potential impact on the processes of cleaning, locking, and unblinding the study database and the timely reporting of the study results. We would appreciate FDA's thoughts on the possibility of a reporting process separated from the processes associated with the main study, and the implications with respect to what would need to be included in the submission dossier.

Section: VI.H. Important Aspects of Data Presentation

Line(s)	Comment
897-898 and footnote 12 (referenced in line 887)	Reference to the 1988 guidance should be replaced by reference to the 2001 CTD guidance. FDA has indicated in other fora that the information previously contained in an ISS may now be addressed within the Summary of Clinical Safety in Module 2, and that an ISS will not be routinely required. In addition, it may not be possible for the sponsor to "fully characterize" the adverse event profile of other drugs in that class. We recommend that the sentence "For a drug that is a new member..." be replaced by "For drugs that are new members of an existing class of drugs, the Summary of Clinical Safety or Integrated Summary of Safety should include a discussion of the known adverse event profile of the class and how this knowledge was used to enhance the development of the new compound".
897-899	In addition to reference to the integrated summary of safety (ISS), the guidance should also refer to the appropriate section within module 2 of the CTD when such an application does not contain an ISS.
920-925	This section indicates that CRFs of subjects who died or discontinued prematurely due to an adverse event should include hospital records, autopsy reports, biopsy reports and radiological reports. While we recognize the potential value of the information in these documents, it should be acknowledged that it may not always be possible to obtain these documents in the current healthcare environment, due at least in part to privacy regulations (HIPAA).

If you have any questions regarding this document, please contact Dr. Judith Sills at (862) 778-2472.

Sincerely,



Judith M. Sills, Pharm.D.
Head, Global Safety Intelligence